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Prague, June 15, 2005

International Bureau of WIPO
34 chemin des Colombettes
1211 Geneva 20
Switzerland

Re: **International Application PCT/CZ2004/000085**
Submission of substitute sheets

Your ref.: **PCT/CZ2004/000085**
Our ref.: **150388/KB**

This is a complement to our reply to the Written opinion mailed April 19, 2005. In accordance with the content of this reply and in compliance with the provision of Article 19, we enclose herewith substitute sheets 7 to 9 amending the original claims.

On behalf of PLIVA-LACHEMA A.S.

Jan Kubát
European patent attorney

Encl.: substitute sheets 7 to 9

PO Box 38
170 04 Prague 7
CZECH REPUBLIC

Přístavní 24
170 00 Prague 7
CZECH REPUBLIC

Tel: +420-2-6671 0172
Fax: +420-2-6671 0174
E-mail: thk@thk.cz
www.thk.cz

Bank: Živnostenská banka
Na Příkopě 20, Prague 1
Account No. 3483-6151 (USD)
3400-6151 (EUR)

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Re: **Applicant's comments on Written Opinion**
International Application PCT/CZ2004/000085

Your ref.: PCT/CZ2004/000085
Our ref.: 150388/KB

The Applicant's comments on the particular items of the Written opinion mailed April 19, 2005 are as coming after.

To make the subject-matter of the present application free of the prior art as objected by the Written Opinion, the Applicant has restricted the invention scope to the preferred invention embodiment composed by combining the original claims 1, 5, 7, 8, 9, and 10 into a new claim 1. The original claims 2, 3, 4, and 6 have been abandoned whereas the original claims 11 to 22 have been renumbered as new claims 2 to 13. Pursuant to the provision of Article 19, the new amended claims are enclosed herewith as substitute sheets 7 to 9. Concerning the original claim 8, the Applicant should like to draw the ISA's attention to that the order indication ".10^3" has been omitted through an oversight behind the quoted amounts of water. The water amounts should in fact read as "980 to 1880 mol, preferably 1280 to 1580 mol" which is supported by the corresponding specific amounts of Example 1: for 1,239 mmol of 7-ethylcamptothecin (and hence for an approximately identical amount of 7-ethyl-1,2,6,7-camptothecin) 1,218 mol

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CZECH REPUBLIC

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170 00 Prague 7
CZECH REPUBLIC

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E-mail: thk@thk.cz
www.thk.cz

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of water is used, which, in turn, means that water is used in an about thousand times larger quantity in respect to 7-ethyl-1,2,6,7-camptothecin. The wording of the new main claim has already been amended in this sense.

In the following, both the novelty and inventiveness of the subject-matter of the newly amended claims (introduced further only as "invention solution") is explained.

1A) Novelty of the invention solution in view of **D1 (WOOD J.L. et al.)**
D1 mentions an oxidation of 1,2,6,7-tetrahydrocamptothecin which is clearly distinct from the oxidation of 7-ethyl-1,2,6,7-tetrahydrocamptothecin as carried out in the framework of the invention solution. The invention solution is thus novel against D1.

1B) Inventiveness of the invention solution in view of **D1 (WOOD J.L. et al.)**
The ISA is of the opinion that *the skilled person, who was looking to solve the problem of providing an alternative method for the production of 7-ethyl-10-hydroxy-camptothecin, would have used the method of D1 in plain analogy with a reasonable expectation of success.* The Applicant, himself, has carried out an experiment in framework of which he oxidized 7-ethyl-1,2,6,7-camptothecin under the conditions as given in D1 (i.e. using 2,91 mol of iodobenzene diacetate, 218 mol of water and 74 mol of acetic acid per 1 mol of 7-ethyl-1,2,6,7-tetrahydrocamptothecin with maintaining the temperature of 34°C for 24 hours and adding iodobenzene diacetate progressively). Whereas these conditions led to an acceptable purity of 10-hydroxycamtothecin in D1, the purity of thus obtained 7-ethyl-10-hydroxycamptothecin was, on the contrary, brutally low (only 80% at yield of 79%). Such a low purity can be hardly taken for the success as above-mentioned by ISA. This fact, itself, testifies in favor of that the concerned 7-substitution can considerably influence the oxidation of the camptothecin molecule and that it could not be predicted on the beforehand for the

skilled person that the conditions as used in D1 for the oxidation of 1,2,6,7-tetrahydro- camptothecin had to be successfully applicable for the oxidation of 7-ethyl-1,2,6,7-tetrahydro-camptothecin, as well. In this regard (low purity as reached), D1 would have rather taught the skilled person working towards obtaining 7-ethyl-10-hydroxycamptothecin with an acceptable purity about 90% from using the oxidation strategy of D1. Despite this, the Applicant surprisingly succeeded in finding out, in general frame of D1 strategy, the conditions under which 7-ethyl-10-hydroxy- camptothecin with acceptable purity (90% at about 90% yield) could be obtained. He reached this by considerably increasing the amounts of water and acetic acid, considerably decreasing the quantity of iodobenzene diacetate, considerably lowering the reaction temperature and considerably shortening the reaction time in comparison with the corresponding conditions of D1. This Applicant's activity can not be regarded as a mere optimizing of conditions for the following reasons: 1) the reaction conditions of the invention solution (the conditions as exemplified include using 1,85 mol of iodobenzene diacetate, 1157 mol of water and 910 mol of acetic acid per 1 mol of 7-ethyl-1,2,6,7-tetrahydrocamptothecin with maintaining the temperature of 22°C for 15 minutes and adding iodobenzene diacetate in one go) are far away from and almost diametrically opposed to those of D1; 2) the reaction conditions of the invention solution go against established rules generally instructing how to simultaneously improve both the yield and purity (especially low reaction temperature and short reaction time), and 3) D1 did not comprise any hint obviously motivating the skilled person to select the reaction conditions as used in the invention solution if 7-ethyl-10-hydroxycamptothecin showing the acceptable purity at the acceptable yield is desired to be obtained. Taking into account the foregoing, the Applicant deems that the invention solution as presently disclosed in the claims is inventive over D1.

2AB) Novelty and inventiveness of the invention solution in view of **D2 (US 4,473,692)**

As opposed to the invention solution disclosing the

oxidation of 7-ethyl-1,2,6,7-tetrahydrocamptothecin leading simultaneously to a direct 10-hydroxy-substitution of the ring A and an aromatization of the ring B, no such combined oxidation effect is the case for D2. The thing is, according to D2 the 10-hydroxy-substitution is realized until after an 1-acyl-10-nitro-substitution occurred. The invention solution is hence novel over D2. Inasmuch D2 did not comprise any hint obviously motivating the skilled person to carry out the oxidation under the conditions as selected while performing the invention solution, the invention solution should be considered inventive over D2.

3AB) Novelty and inventiveness of the invention solution in view of **D3 (US 5,734,056)**

D3 includes as intermediate step an oxidation of 1,2,6,7-tetrahydrocamptothecin rather than that of 7-ethyl-1,2,6,7-tetrahydrocamptothecin as it is the case of the invention solution. The invention solution is thus novel over D3. Taking into account that D3 (especially Example 6 thereof) substantially repeats the oxidation conditions as described in D1, the inventiveness of the invention solution can be supported with the same argumentation as already displayed in 1B).

4A) Novelty of the invention solution in view of **D4 (WO 2004/100897)**.

As D4 has been published until after the filing date of the present application this should not be able to infringe the inventiveness of the invention solution. So the following discussion does not concern but the novelty of the invention solution over D4. The scope of D4 as presently defined for the oxidation of 7-ethyl-1,2,6,7-camptothecin in claims 2 to 8 evidently implies prior art as also objected against the invention solution. In addition, claim 2 of D4 is improperly broad (no oxidation conditions are mentioned therein at all). For these reason, the oxidation scope of D4's claim 2 is supposed to be amended during further procedure to the effect that it is free of the concerned prior art and comprises the oxidation condition being closed to (i.e. supported by) the only example of D4 dealing with the oxidation of 7-ethyl-1,2,6,7-camptothecin. Only after this is done, a proper oxidation scope of D4

will be clearly defined and so able to be compared with the invention solution. Nevertheless already now, it can be said the oxidation process of D4 is clearly different from that of the invention solution. This difference is evident from the following comparison: the invention solution uses from 0,99 to 1,85 mol of iodobenzene diacetate (as opposed to 2,55 mol of D4), from 668 to 1001 mol of acetic acid (as opposed to 197 mol of D4), from 980 to 1880 mol of water (as opposed to 627 mol of D4), temperature of from 15 to 30°C (as opposed to 10°C of D4), and reaction time of from 10 to 15 minutes (D4 does not include any mention of the used reaction time but this is supposed to exceed at least one hour). The Applicant is therefore convinced that D4 will be considered not able to infringe the novelty of the invention solution if the novelty objection arises in any regional phase.

In the foregoing, the argumentation supporting the patentability of the invention solution has been substantially focused on the oxidation process as presently disclosed in claim 1. As to the hydrogenation process being now disclosed in the dependent claims 2 to 13, its novelty and inventiveness having to be only assessed in combination with the preceding oxidation of claim 1 seem to be also incontestable.

As far as the absence of the closest prior art in the description of the present application is concerned the Applicant is prepared to avoid this defect as soon as he is enabled to act so.

On behalf of PLIVA-LACHEMA A.S.

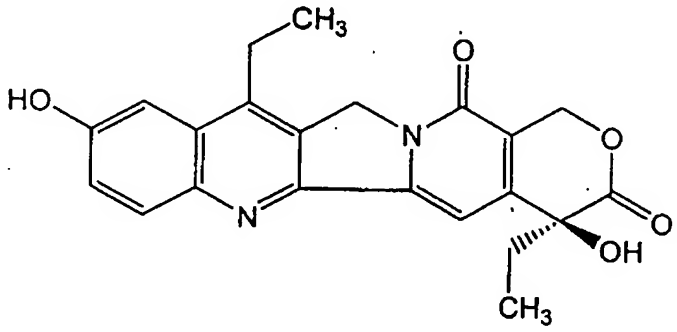
Jan Kubát

European patent attorney

Encl.: substitute sheets 7 to 9

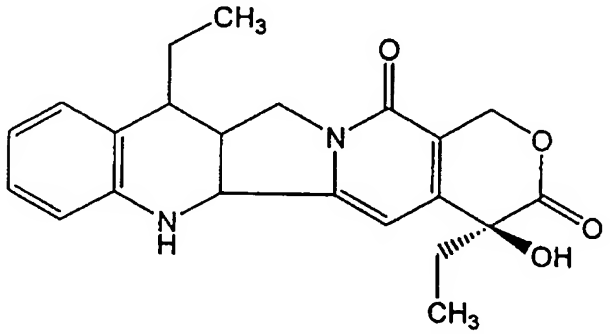
C L A I M S

1. The method of manufacturing of 7-ethyl-10-hydroxy-camptothecin of formula I



(I)

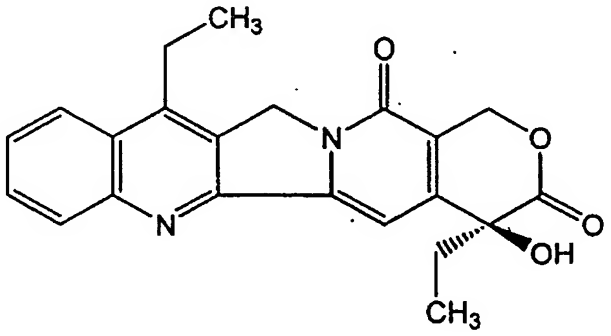
characterized in that 7-ethyl-1,2,6,7-tetrahydrocamptothecin of formula IV



(IV)

is oxidized with iodobenzene diacetate in acetic acid and in the presence of water under the conditions consisting in that iodobenzene diacetate is used in an amount of 0.99 to 1.85 mol per 1 mol of 7-ethyl-1,2,6,7-tetrahydrocamptothecin, acetic acid is used in an amount of 668 to 1001 mol per 1 mol of 7-ethyl-1,2,6,7-tetrahydrocamptothecin, water is used in an amount of 980 to 1880 mol per 1 mol of 7-ethyl-1,2,6,7-tetrahydrocamptothecin and the oxidation is carried out at a temperature from 15 to 30 °C for 5 to 30 minutes.

2. The method according to claim 1, **characterized in that** the starting 7-ethyl-1,2,6,7-tetrahydrocamptothecin is obtained by hydrogenation of 7-ethylcamptothecin of formula II



(II)

in a saturated aliphatic monocarboxylic acid having 1 to 3 carbon atoms, using hydrogen in the presence of a hydrogenation catalyst and a sulfur compound that partly deactivates the hydrogenation catalyst.

3. The method according to claim 2, **characterized in that** the saturated aliphatic acid is formic acid, acetic acid or trifluoroacetic acid.

4. The method according to claim 3, **characterized in that** acetic acid is used in an amount of 791 to 1187 mol, preferably 890 to 1088 ml, per 1 mol of 7-ethylcamptothecin.

5. The method according to claim 2, **characterized in that** the sulfur compound that partly deactivates the hydrogenation catalyst is dimethyl sulfoxide.

6. The method according to claim 5, **characterized in that** dimethyl sulfoxide is used in an amount of 0,18 to 0,33, preferably 0,23 to 0,28 ml, per 1 mol of 7-ethylcamptothecin.

7. The method according to claim 2, **characterized in that** the hydrogenation catalyst is a noble metal.

8. The method according to claim 7 **characterized in that** the noble metal is platinum.

9. The method according to claim 8, **characterized in that** platinum is used on an activated carbon or aluminium oxide carrier.

10. The method according to claim 9, **characterized in that** platinum is used in an amount of 0,018 to 0,027 mol, preferably 0,020 to 0,025 mol, per 1 mol of 7-ethylcamptothecin, in form of a hydrogenation catalyst, formed by platinum on an activated carbon with platinum content 5 %.

11. The method according to claim 2 **characterized in that** the hydrogenation is carried out at a pressure from 0,3 to 0,7 MPa, preferably at a pressure from 0,4 to 0,6 MPa.

12. The method according to claim 11, **characterized in that** the hydrogenation is carried out at a temperature from 45 to 85 °C, preferably at 58 to 72 °C.

13. The method according to claim 11, **characterized in that** the hydrogenation is carried out for 24 to 70 hours, preferably for 40 to 50 hours.